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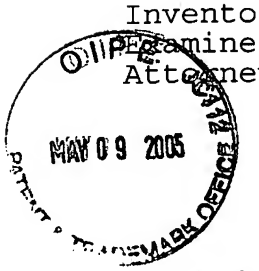
FEE TRANSMITTAL

Application Number 10/680,649 Art Unit 1614
Filing Date October 7, 2003 Confirmation No. 5089
Inventor(s) Robert A. Holton
Examiner Name Cybille Delacroix Muirhei
Attorney Docket Number FSUM 10442.19



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FSUM 10442.19
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Robert A. Holton
Serial No. 10/680,649
Filed October 7, 2003
Confirmation No. 5089
For TAXANE FORMULATIONS
Examiner Cybille Delacroix Muirhei

Art Unit 1614

BRIEF FOR APPELLANTS

Anthony R. Kinney, Reg. No. 44,834
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

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TABLE OF AUTHORITIES

REFERENCES

CASES

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Robert A. Holton
Serial No. 09/776,492
Filed February 2, 2001
Confirmation No. 2712
For C10 ESTER SUBSTITUTED TAXANES
Examiner Ba K. Trinh

Art Unit 1625

BRIEF FOR APPELLANTS

This is an appeal from the final rejection of the above-identified application made in the Office action mailed November 9, 2004 and the Advisory Action dated March 24, 2005, together rejecting claims 1-20. The appealed claims are presented in the Appendix to this brief, attached hereto. A Notice of Appeal was mailed on March 9, 2005.

I. REAL PARTY IN INTEREST

The real party in interest is Florida State University, owner of a 100 percent interest in the pending application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any pending appeals or interferences which may directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-20 are pending in this application. The claims on appeal are set forth in full in the Appendix to this Brief.

Claims 1-20 stand rejected as being unpatentable under 35 U.S.C. 103(a) over Broder et al. (U.S. Patent No. 6,395,770) and McChesney-Harris (U.S. App. No. 2001/0029264 A1) in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

V. SUMMARY OF THE INVENTION

The present invention is generally drawn to methods of treating a patient afflicted with a cancer by administrating pharmaceutical compositions containing a taxane that compare favorably to Taxol® (paclitaxel) and Taxotere® formulations with respect to efficacy as anti-tumor agents with respect to toxicity and stability.

In particular, the present invention is directed to methods of treating a patient afflicted with a cancer by orally administering pharmaceutical compositions containing a taxane and a pharmaceutically acceptable solvent that can dissolve the taxane, wherein the taxane has a solubility in ethanol of at least 100 mg/ml.

VI. ISSUE

The only issue presented on appeal is whether claims 1-20 are unpatentable under 35 U.S.C. § 103(a) over Broder et al. (U.S. Patent No. 6,395,770) and McChesney-Harris (U.S. App. No. 2001/0029264 A1) in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

VII. GROUPING OF CLAIMS

For purposes of this appeal, claims 1-20 do not stand or fall together. The claims have been divided into two groups: Group I (claims 1-6, 10-11, and 18-20) and Group II (claims 7-9 and 12-17). The claims of Group I and Group II are separately and independently patentable for the reasons described in Sections VIII(A)(1) and VIII(A)(2), *infra*.

VIII. ARGUMENT

A. The Office has Failed to Establish a *Prima facie* Case that Claims 1-20 are Obvious Under 35 U.S.C. 103(a)

According to the Office, the claims of the present application are obvious under 35 U.S.C. § 103(a) over Broder et al. (U.S. Patent No. 6,395,770) and McChesney-Harris (U.S. App. No. 2001/0029264 A1) in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

The Office cites Broder et al. for disclosing the oral administration of a "taxane class of antineoplastic agents, in particular, paclitaxel and its derivatives, analogs and prodrugs and the semisynthetic paclitaxel analog docetaxel."[1] The Office further cites Broder et al. as disclosing that the orally administrable therapeutic agents may include "paclitaxel, other taxanes, docetaxel and derivatives and prodrugs of all of the forgoing, particularly their 2'-MPM salts and other 2'-methylpyridinium salts."[2]

The Office cites McChesney-Harris as disclosing "novel methods and compositions for delivery of paclitaxel and other derivatives or their water insoluble derivatives."[3]

The Office argues that "absent evidence to the contrary" the broad genus of taxanes and water insoluble derivatives (other than paclitaxel) disclosed by Broder et al. and McChesney-Harris "would obviously, if not inherently, exhibit the claimed solubility in ethanol, *i.e.*, at least 200 mg/ml." The Office further asserts that Applicant has not distinguished the class of drugs disclosed by Broder et al. and McChesney-Harris from the claimed taxanes.

In order to make out a *prima facie* case of obviousness under 35 U.S.C. §103 in view of prior art, the prior art references must individually or in combination disclose or

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[1] Office action mailed November 9, 2004, page 4, citing Broder et al., U.S. Pat. No. 6,395,770, col. 6, lines 23-28.

[2] *Id.*, citing Broder et al., U.S. Pat. No. 6,395,770, col. 7, lines 20-26.

[3] *Id.*, citing McChesney-Harris, U.S. App. No. 2001/0029264 A1, paragraph 0009.

suggest all of the limitations of the claim. The references must also suggest or provide a motivation to one skilled in the art to modify the cited references or combine their teachings. Finally, one skilled in the art, upon reading the prior art references, must have a reasonable expectation of success in modifying or combining the references.[4]

In this case, a *prima facie* case of obviousness has not been established because the Office failed to identify prior art that, individually or in combination, disclose all the limitations of the claims. The Office has further failed to make any showing that the cited art would motivate or suggest to one skilled in the art to combine all the required elements of the claims. Finally, the Office has failed to show how one skilled in the art would have a reasonable expectation of success in combining the references.

1. The Group I Claims (claims 1-6, 10-11, and 18-20)

Claim 1 is representative of the Group I claims. Claim 1 is directed to a method of treating a patient afflicted with a cancer selected from the group consisting of breast, head, neck, esophageal, lung, and colon cancer by orally administering a pharmaceutical composition consisting essentially of a taxane, a solvent capable of dissolving the taxane, polyoxyethylatated castor oil, a diluent, and optionally a flavoring, wherein the taxane has a solubility in ethanol at room temperature of at least 200 mg/ml.

Applicant discloses that it is believed that the ethanol solubility of the antitumor compound may be directly related to its efficacy.[5] Thus, by selecting taxane compounds having a solubility in ethanol at room temperature of at least 200 mg/ml, an effective method of treating cancer can be formulated.

Broder et al. describe a method for making an orally administrable taxane bioavailable to human patients at a level sufficient to treat taxane-responsive conditions by orally co-administering a taxane and an oral bioavailability enhancing agent

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[4] MPEP §§ 2143-2143.03.

[5] Specification, page 44, lines 33-35.

comprising a cyclosporin. All working examples of Broder et al. utilize paclitaxel as the taxane component.[6] While Broder et al. generally disclose that taxanes and derivatives thereof may be used, the specification emphasizes the use of paclitaxel.

Broder et al. do not disclose or quantify the solubility of taxanes in ethanol or suggest any benefit of selecting a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml. Rather, Broder et al. disclose at length in the specification and the working examples the preferential use of paclitaxel, a compound having a solubility in ethanol of less than 40 mg/ml and the beneficial coadministration of a bioavailability enhancing agent comprising a cyclosporin.[7] While Broder et al. mentions that other taxane compounds may be used, the reference is silent regarding quantifying the solubility of taxane compounds in ethanol, or suggesting a relationship between the antitumor efficacy of a taxane compound and its solubility in ethanol. Thus, one skilled in the art reading Broder et al. would not be motivated by Broder et al. to even investigate the solubility properties of taxane compounds in ethanol, let alone identify and select a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml for a method of treating cancer.

McChesney-Harris is directed to formulations that improve the water solubility of taxane compounds. McChesney-Harris disclose that water solubility is an obstacle in the administration of paclitaxel as it tends to precipitate when placed in an aqueous solution.[8] McChesney-Harris describes compositions for treating taxane-responsive conditions wherein the compositions comprise paclitaxel and other taxanes or their water insoluble derivatives, Vitamin E-TPGS, and an organic solvent.[9] The disclosed compositions are designed to overcome the water solubility problems of taxanes while

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[6] Broder et al., U.S. Pat. No. 6,395,770, Examples 1-4.

[7] *TAXOL Science and Applications*, Edited by Matthew Suffness, CRC Press, ISBN0-8493-8382-X, Chapter 9 Biopharmaceutics of paclitaxel (taxol): Formulation, activity, and pharmacokinetics, page 238, written by Robert Straubinger

[8] McChesney-Harris, U.S. Pub. No. 2001/0029264, paragraphs [0006].

[9] McChesney-Harris, U.S. Pub. No. 2001/0029264, paragraphs [0009] and [0012].

avoiding toxicity problems of CHREMOPHOR® EL which the prior art used to solubilize water insoluble taxanes.[10]

While McChesney-Harris generally discloses a taxane composition for treating taxane-responsive conditions, paclitaxel is the only taxane species which is specifically disclosed. While McChesney-Harris discloses a taxane composition formulated by mixing a taxane with d-alpha-tocopheryl polyethylene glycol 100 succinate (Vitamin E-TPGS) and an organic solvent such as ethanol, the benefits of solubility in ethanol or the relationship between improved taxane efficacy and its solubility in ethanol are not disclosed or suggested. [11]

Goodman and Gillman disclose that paclitaxel has very limited solubility and must be administered in a vehicle of 50% ethanol and 50% polyethoxyethylated castor oil.[12] Goodman and Gillman do not address oral administration of taxanes; rather, they only discuss the administration of paclitaxel in the form of infusions. Furthermore, Goodman and Gillman do not disclose or suggest a relationship between a taxane's improved efficacy for treating cancer and its solubility in ethanol.

All Elements of Claim 1 are not Disclosed in Cited References

The Office asserts that it would be obvious or inherent that the disclosed taxanes and water soluble derivatives would exhibit the claimed solubility. None of the cited references, however, disclose or suggest a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml. None of the references suggest that a direct correlation exists between a taxane's solubility in ethanol and its effectiveness in treating cancer. Thus, without more, selection of a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml is not disclosed or suggested.

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[10] *Id.*, paragraph [0006].

[11] *Id.*, paragraph [0022].

[12] Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition, 1260.

Contrary to the Office's assertion, the general disclosure of the chemical group of taxanes without more does not render the claimed element obvious merely because a claimed element may be inherent in some compounds of the disclosed genus:

> [T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.[13]

Thus, an undisclosed taxane having an unrecognized advantage of a solubility in ethanol at room temperature of at least 200 mg/ml cannot support an obviousness rejection of claim 1.

No Motivation is Disclosed or Suggested to Combine Elements of Claim 1

The cited references fail to disclose or suggest a motivation to combine all the elements of claim 1. As discussed above, none of the cited references disclose a taxane that has a solubility in ethanol at room temperature of at least 200 mg/ml. Furthermore, none of the cited references disclose or suggest that increased ethanol solubility of a taxane may be directly related to improved efficacy in treating cancer. Both Broder and McChesney-Harris disclose compositions to improve absorption and/or water solubility of taxane wherein a second compound is used to increase the bioavailability or water solubility of taxane (e.g. Broder et al.'s use of cyclosporin and McChesney-Harris's use of Vitamin E-TPGS). The references, at most, disclose that taxane insolubility in water is an obstacle to absorption or bioavailability, which is not equivalent to disclosing that improved ethanol solubility of a taxane is directly related to its efficacy in treating cancer. Thus, the Office has not articulated how the prior art provides any motivation to one skilled in the art to combine the elements of claim 1.

McChesney-Harris discloses that prior art attempts to change the "chemical structure of paclitaxel can potentially decrease the antitumor activity of the drugs, and

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[13] *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A 1977)(quoting *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966)). *See also In re Naylor*, 369 F.2d 765, 768, 152 U.S.P.Q. 106, 108 (C.C.P.A. 1966) ("[Inherency] is quite immaterial if . . . one of ordinary skill in the art would not appreciate or recognize that inherent result."); *In re Rijckaert*, 9 F.3d 1531, 1533, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).

does not address the problem of low stability and short shelf life."[14] The modification of paclitaxel disclosed by McChesney-Harris was an attempt to increase its water solubility, **not** its ethanol solubility. Thus, prior art attempts to modify the structure of paclitaxel were not related to Applicant's understanding that improved ethanol solubility of taxane compounds are directly related to improved efficacy in treating cancer, but rather related to overcoming the obstacle of paclitaxel's precipitation in an aqueous solution. Furthermore, because McChesney-Harris disclose that modifying paclitaxel resulted in decreased efficacy in treating cancer, contrary to the Office's assertion, one skilled in the art reading McChesney-Harris or the prior art therein would be led away from modifying taxane compounds to increase their solubility properties.

The Office vaguely asserts that one skilled in the art would be motivated by a reasonable expectation of success to modify the compositions disclosed by Broder et al. and McChesney-Harris such that the taxane would be sufficiently soluble to be therapeutically effective.[15] However, obviousness under 35 U.S.C. 103(a) requires a motivation to modify references and a reasonable expectation of success, not a motivation by a reasonable expectation of success. A "reasonable expectation of success" by itself is not a valid source of motivation. Rather, "[t]here are three possible sources for a motivation to combine references: The nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art."[16]

The Office appears to be utilizing impermissible hindsight reconstruction by essentially asserting that since Applicant has successfully described the method of claim 1, one skilled in the art would likewise be motivated by an expectation of success to modify the compositions of disclosed by Broder et al. and McChesney-Harris, which do not disclose all the claimed elements, to derive the claimed method with all its elements. Without using impermissible hindsight reconstruction, however, one skilled

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[14] *McChesney-Harris*, U.S. Application Publication No. 2001/0029264A1, paragraph [0007].

[15] Office action mailed November 9, 2004, page 5.

[16] *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998); MPEP § 2143.01.

in the art would not have any reasonable expectation of success. The Office has not, and cannot, point to any disclosure or suggestion in the art, other than Applicant's, which provides such an expectation.

No Reasonable Expectation of Success

The cited art is devoid of any disclosure that suggests that the solubility of a taxane compound in ethanol is directly related to its efficacy in treating cancer. Without such a disclosure or suggestion, one skilled in the art would have no reasonable expectation of success in combining references to produce Applicant's method of treatment since it would not be known, without hindsight reconstruction, what a successful combination would be.

Initial Burden of Proof to Factually Support Obviousness Rejections is Unmet

The Office has failed to meet its initial burden of providing factual support for its obviousness rejections. The Office asserts that since Broder and McChesney-Harris generally disclose the use of taxanes, such taxanes would, "absent evidence to the contrary, . . . obviously, if not inherently, exhibit the claimed solubility in ethanol."[17] The Office further asserts that "[a]bsent evidence to the contrary," one skilled in the art would be motivated by an expectation of success to modify the compositions such that the taxane was sufficiently soluble to be therapeutically effective.[18]

The concept of *prima facie* obviousness allocates the burden of producing evidence during the examination process. "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness."[19] However, the Office repeatedly asserts the claims are obvious "absent evidence to the contrary," without providing specific factual support of the assertion. By doing so, the Office is improperly attempting to shift the burden of proof to the applicant to prove the patentability of the

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[17] Office action, page 4, paragraph 2, emphasis added.

[18] Office action, page 5, paragraph 1, emphasis added.

[19] MPEP § 2142, emphasis added.

claims without first meeting its burden of factually supporting any *prima facie* conclusion of why the claimed invention is unpatentable. The phrase "absent evidence to the contrary," instead of supporting an obviousness rejection, indicates that the Office cannot find prior art necessary to factually support their improper conclusion of obviousness. Applicant has filed claims which are believed to be patentable. It is the Office's initial obligation to provide evidence that factually supports an obviousness rejection. Absent such evidence, no shift of burden occurs, and Applicant is under no obligation to submit evidence of non-obviousness.[20]

For the reasons provided above, a *prima facie* case of obviousness has therefore not been established with respect to the Group I claims.

2. *The Group II Claims (claims 7-9 and 12-17)*

Claim 7 is representative of Group II claims. It is dependent upon claim 1 and is patentable for the same reasons as those stated above with respect to claim 1. It is separately and independently patentable over Broder et al., McChesney-Harris, and Goodman & Gilman's for the following reasons.

Claim 7 requires the taxane of claim 1 to have an ID_{50} value determined relative to an HCT116 cell line that is at least 4 times less than that of paclitaxel. Applicant discloses that it is preferred that an antitumor compound have an ID_{50} value (i.e., the drug concentration producing 50% inhibition of colony formation) of at least 4 times less than that of paclitaxel.[21]

None of the cited references compare relative efficacy of different taxane compounds on the inhibition of cancer cell lines. While Broder et al. and McChesney-Harris disclose that the taxane genus of compounds may be used, both references disclose at length in the specification and the working examples the preferential use of paclitaxel, Goodman & Gilman also fail to compare the relative efficacy of different taxane compounds in an oral composition.

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[20] MPEP § 2142.

[21] Specification, page 45, lines 3-7 and Examples 5, 10, 15, 20, 25, 30, 35, and 40.

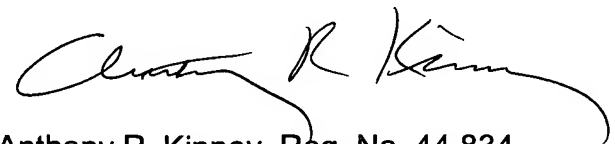
The cited references fail to disclose or quantify relative cancer cell inhibition efficacies of different taxane compounds compared to paclitaxel. One skilled in the art reading the cited references would therefore not be motivated to compare and select a taxane that has an HCT116 ID_{50} concentration that is at least four times less that of paclitaxel. For this reason and further for the reasons as those set forth above for Group I claims, Group II claims are non-obvious under 35 U.S.C. 103(a) over the cited references.

B. Conclusion

A *prima facie* case of obviousness has not been established pursuant 35 U.S.C. § 103(a). It has not been shown that the cited references can be properly combined or, when considered as a whole, would have taught or suggested all the limitations of the claimed invention. For these reasons, and for those more fully stated above, Applicant respectfully requests the Examiner's rejections be reversed and claims 1-20 be allowed.

A check for $620 is enclosed ($500 for the appeal brief fee specified under 37 C.F.R. 41.20(b)(2) and $120 for a one month extension of time fee specified under 37 C.F.R. 1.17(a)(1)). The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,



Anthony R. Kinney, Reg. No. 44,834
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

ARK/leb
*Enclosure
Express Mail No. EV 455483958 US

APPENDIX

1. A method of treating a patient afflicted with cancer selected from the group consisting of breast, head, neck, esophageal, lung, and colon cancer, the method comprising oral administration of a pharmaceutical composition to the patient, the pharmaceutical composition consisting essentially of

(a) a taxane;

(b) a solvent capable of dissolving the taxane;

(c) polyoxyethylated castor oil;

(d) a diluent; and

(e) optionally, a flavoring;

wherein the taxane has a solubility in ethanol at room temperature of at least 200 mg/ml.

2. The method of claim 1 wherein the composition contains a flavoring.

3. The method of claim 1 wherein the solvent capable of dissolving the taxane is ethanol.

4. The method of claim 1 wherein the diluent is water, saline, dextrose or an electrolyte solution.

5. The method of claim 1 wherein the solvent capable of dissolving the taxane is ethanol and the diluent is saline.

6. The method of claim 5 wherein the ethanol and polyoxyethylated castor oil are present in a volumetric ratio of about 1 to 1.

7. The method of claim 1 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 4 times less than that of paclitaxel.

8. The method of claim 1 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 7 times less than that of paclitaxel.

9. The method of claim 1 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 10 times less than that of paclitaxel.

10. The method of claim 1 wherein the taxane has a solubility in ethanol at room temperature of at least 500 mg/ml.

11. The method of claim 1 wherein the taxane has a solubility in ethanol at room temperature of at least 800 mg/ml.

12. The method of claim 10 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 4 times less than that of paclitaxel.

13. The method of claim 10 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 7 times less than that of paclitaxel.

14. The method of claim 10 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 10 times less than that of paclitaxel.

15. The method of claim 11 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 4 times less than that of paclitaxel.

16. The method of claim 11 wherein the taxane has an ID_{50} value determined relative to an HCT116 cell line that is at least 7 times less than that of paclitaxel.

17. The method of claim 11 wherein the taxane has an ID_{50} value determined relative toan HCT116 cell line that is at least 10 times less than that of paclitaxel.

18. The method of claim 1 wherein the cancer is breast cancer.

19. The method of claim 1 wherein the cancer is esophagus cancer.

20. The method of claim 1 wherein the cancer is colon cancer.